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Development and Optimization of Fast Dissolving Film of Losartan Potassium

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ABSTRACT

The present work aims to prepare fast dissolving films of Losartan Potassium with purpose of developing rapid onset of action, which is very convenient for administration without using water. Fast dissolving films are meant to be dissolved in saliva and remain in oral cavity until swallowed. The films were prepared by solvent casting method and characterized by UV, DSC studies. The plasticizer concentration was selected on the basis of flexibility, tensile strength and stickiness of the film. In the present study polyethylene glycol was used as plasticizes. Fast dissolving films were evaluated for drug content and the drug loading capacity. The dissolution profile and folding endurance were found to be satisfactory. The disintegration time of formulation F3 film was lowest (30 sec), so they release drug faster than other formulations. A drug-excipients interaction was performed by DSC and FTIR; results were shown that there was no interaction between drug and excipients used. In vitro release mechanism was evaluated by subjecting the dissolution data to various kinetic models and the drug release was found to best fit the Korsemeyer-peppas model. Hence it is concluded that Losartan Potassium fast dissolving films are successfully developed and evaluated.

Key Words: Fast dissolving films, Losartan Potassium, Solvent casting method, Hypertension

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INTRODUCTION

The oral route is the most acceptable drug delivery route for patient compliance aspects. There are many drug delivery systems available that are used for the administration of drugs by oral route. All these oral drug delivery systems are associated with their own merits and demerits. Research and development in the oral drug delivery field has leads to transition of dosage forms from simple conventional tablets/capsules, modified release tablets/capsules, oral disintegrating tablet, wafer and recent development of oral fast dissolving films[1]. These fast dissolving films contain active pharmaceutical ingredient embedded in the matrix of film forming polymers in the presence of other excipients. The advantages of convenience of dosing and portability of fast dissolving oral thin films have lead to wider acceptability of this dosage form by pediatric as well as geriatric population equally.

The need for the fast dissolving oral films has been felt because of the variety of reasons. Fast dissolving oral films represent the category of dosage forms that offers high patient compliance especially for the patients having difficulty in swallowing or chewing. Oral administration of a drug can be made without the use of water and hence it can be taken anywhere anytime. This dosage form is a very good substitute for the liquid dosage forms and hence is suitable for pediatric and geriatric patients. Moreover, fast dissolving films are also devoid of friability problems associated with orodispersible tablets.

Losartan Potassium is an angiotensin II receptor antagonist drug used mainly to treat high blood pressure (hypertension). It may also delay progression of diabetic nephropathy and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes, hypertension and microalbuminuria (>30 mg/24 hours) or proteinuria (>900 mg/24 hours). Average daily dose of Losartan Potassium is Initially 50 mg once daily. If BP is not adequately controlled, increase dosage to 100 mg once daily[2]. Fast dissolving film of Losartan Potassium will prove to be a very convenient dosage form not only for the children, aged or mentally challenged patients but also for the patients who are travelling or are in similar conditions.

Fast dissolving films can be prepared by solvent casting method Hydroxypropyl methylcellulose (HPMC) is a well known film forming polymer. It has been found to retain its film forming properties in the presence of other excipients although nature and concentration of excipients will modify its film forming ability. The oral thin films must possess certain characteristics both from stability and patient convenience point of view.

The present research work involves the formulation development of fast dissolving films of

Losartan Potassium by applying full factorial design to understand the effect of formulation variables like concentration of HPMC E-15, HPMC E-5, microcrystalline cellulose (MCC), polyethylene glycol (PEG) 400, citric acid and mannitol on physicomechanical, properties of the film like, thickness, folding endurance, tensile strength, surface pH etc. Effect of these formulation variables on disintegration time, content uniformity, in vitro dissolution rate and stability were also studied[4].

MATERIALS AND METHODS

Losartan Potassium was gifted to us by Alembic pharmaceuticals; Baroda, Gujarat.HPMC E-15, HPMC E-5and Micro crystalline cellulose (MCC) were procured from Merck India Ltd., Mumbai. Organic solvents used were of analytical grade and other chemicals of Laboratory grade.

Preparation of fast dissolving films

The fast dissolving films of losartan potassium were prepared by the solvent casting technique using HPMC E-15 and HPMC E-5.PEG 400 as a plasticizer. MCC was used as a superdisintegrants. Citric acid as saliva stimulating agent, Mannitol as a sweetening agent. The fast dissolving films of losartan potassium were formulated by solvent casting method, by dissolving weighed quantity of drug in required volume of water. The selected concentration of polymers added to another beaker and dissolve by adding sufficient amount of water. Then both the solution was mixed together. Initially stirring was carried out at low RPM and later at higher speed. The required quantity of plasticizer was added drop wise. The solution was casted on to Petri dish (area of 64 cm^2)within inverted funnel and allowed to dry overnight at room temperature. The films were removed carefully and circular patches of 2 × 2 cm diameter (an area of 4 cm^2)were punched out so that each patch contained 4 mg of the drug[3].

Table – 1. Formulation of losartan potassium fast dissolving film (Weight in mg)

Formula	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan Potassium	50	50	**50**	50	50	50	50	50	50
HPMC E-15	150	200	**250**	150	200	250	150	200	250
HPMC E-5	50	50	**50**	50	50	50	50	50	50
MCC	50	50	**50**	75	75	75	100	100	100
Citric Acid	50	50	**50**	50	50	50	50	50	50
Mannitol	50	50	**50**	50	50	50	50	50	50
PEG 400 (%w/w)	30	30	**30**	30	30	30	30	30	30
Purified water (ml)	10	10	**10**	10	10	10	10	10	10

EVALUATION OF FAST DISSOLVING FILMS

Film thickness:

The thickness was measured using a micrometer screw gauge at three different position of the film and the average thickness was determined as shown in Table– 2[5].

Uniformity of weight:

The film (4 cm^2) was cut at three different place. The weight of each film strip was taken and weight variation was calculated[5, 6].

Surface pH:

Surface pH of the films was determined in order to investigate the possible side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The film was placed in a Petri dish and moistened with 0.5 ml of distilled water and kept for 1 h. pH was noted with the electrode of the pH meter. The average of three determinations for each formulation was done[7].

Folding Endurance:

The folding endurance was expressed as the number of folds (number of times the film is folded at the same place) required to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip of 2 × 2 cm diameter (an area of 4 cm^2) was subjected to folding endurance by folding the film at the same place repeatedly several times until a visible crack was observed, and the values were reported[9, 10].

Drug content:

This parameter was determined by dissolving film of 2 × 2 cm diameter(an area of 4 cm^2) containing 4 mg of losartan potassium in 50 ml simulated salivary fluid with occasional shaking Filtration was carried out to remove insoluble residue, 1 ml of the filtrate was diluted to 10 ml with simulated saliva fluid. The absorbance was measured at 250 nm using an UV spectrophotometer. The experiments were carried out in triplicate for the films of all formulations and average values were recorded as shown in Table– 2[5, 9.]

Composition of simulated salivary fluid [7]

Ingredients	Quantity
Disodium hydrogen phosphate (Na_2HPO_4)	2.38 g
Potassium dihydrogen phosphate (KH_2PO_4)	0.19 g
Sodium Hydroxide(NaOH)	8.00 g
Distilled Water	Up to 1000ml
Phosphoric acid	q.s to pH 6.8

Tensile Strength Measurement:

This mechanical property was evaluated using Instron universal testing instrument (Model 1121, Instron Ltd., Japan) with a 5-kilogram load cell. Film strips in special dimension and free from

air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp at a rate of 100 mm/min; the force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Two mechanical properties, namely tensile strength and % elongation were computed for the evaluation of the film. Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and cross sectional area of fractured film as described from the following equation [7,8].

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross sectional area of the sample (mm 2)}}$$

Percent elongation can be obtained from the following equation:

$$\%\text{Elongation at break} = \frac{\text{Increase in length}}{\text{Original Length}} \times 100$$

Values for tensile strength and percentage elongation for all formulations are shown in Table - 3.

Disintegration test:

Disintegration test was performed to ensure the disintegration of the film in water. film from each formulation was introduced into disintegration apparatus IP. A disc was added into the tube. The assembly was suspended in a beaker containing simulated saliva and the apparatus was operated until the film disintegrated. Test was performed in triplicate[5, 11].

In-vitro dissolution study

The dissolution test was performed according to USP type-I basket apparatus (Electolab, Mumbai). Test solution was 900 mL of simulated salivary fluid pH 6.8 at 37±0.5°C with a rotation rate of 50 rpm. 10 ml aliquots of samples were taken at every 1min and replaced with the same. Losartan potassium was assayed spectrophotometrically at 250 nm (UV-Thermo scientific). The results were expressed as each value is the mean ± SD, n = 3 determinations.[5,8,12]

Kinetic analysis of *in vitro* release data:

In order to determine the release mechanism that provides the best description pattern of drug release, the *in vitro* release data were fitted to zero-order, first-order and Higuchi matrix model. The release data were also kinetically analyzed using the Korsmeyer–Peppas model. The release exponent (n) describing the mechanism of drug release from the matrices was calculated by regression analysis using the following equation. Mt/ M = Kt Where Mt/M is the fraction of drug released (using values of Mt/M within the range 0.10–0.60) at time t and K is a constant

incorporating the structural and geometric characteristics of the release device. A value of n=0.5 indicates case I (Fickian) diffusion, 0.5<n<1 indicates anomalous (non-Fickian) diffusion, and n=1 indicates case II transport (Zero order release), n>1 indicates Super case II transport. From the mathematical treatment of the in vitro release data of losartan potassium from fast dissolving films, the values of R^2 (coefficient of determination) has been obtained as presented in Table - 5.[7,14]

Stability studies

The film formulations were also subjected to stability studies by kept them for 8 weeks under environmental conditions such as room temperature of 27 ± 2 °C/65% RH, oven temperature of 40 ± 2 °C/75% RH and in the refrigerator at 4–8 °C. At the end of the period, drug content, swelling index, surface pH, and release profiles were determined.[5, 13, 15]

Drug – Polymer interaction studies:

The losartan potassium drug &F3 film were subjected to thermal analysis by Differential Scanning Calorimetry (DSC) to confirm the absence of any interactions. Instrument Model no-DSC-60, Temp range-50^0C-300^0C, Rate – 20^0C per min., Atmosphere Air and Made by-shimadzu corporation, Japan.[8]

RESULTS AND DISCUSSION:

Losartan potassium fast dissolving films were designed with the objective of fast, improved patient compliance and better bioavailability. Therefore, rapidly water-soluble polymers such as HPMC E-15 and HPMC E-5 were chosen for the formulation with PEG 400 for conferring plasticity properties.

All the prepared film were smooth, almost transparent with good flexibility. It was observed that uniformity of weight, thickness were found to be satisfactory

Surface pH:

The surface pH was close to neutral in all the formulations, and this means that they may have less potential to irritate the buccal mucosa, therefore more comfortable.

Folding endurance:

All film formulations exhibited good folding endurance exceeding 25-100, indicating that they are tough and flexible.

Disintegration time:

The disintegration time of films was found to be decreased with increase in the concentration of the HPMC E-15 polymer. When placed over the tongue, the film dissolved instantly. The

disintegration time of formulation F3 film was lowest, so they release drug faster then other formulation.

Drug content:

All the formulations of losartan potassium containing HPMC E-15, HPMC E-5 and PEG 400 polymers show uniform drug content as seen in Table - 2.

***In vitro* dissolution studies:**

In vitro drug release study was carried out using USP dissolution apparatus, type-I. Comparative dissolution profile of all batches is given in Figure - 1. Being the fast disintegrating formulations the release rates of all the formulations were very rapid. Formulation F3 released losartan potassium completely faster. This may be due to HPMC E-15, MCC and PEG 400 that result in increase wettability and penetration of water into the film matrices and hence increased diffusion of the drug. Whereas release rates of other formulation were comparatively slowest.

Table – 2. Physical characterization of film formulations

code	Thickness (mm) of 4cm^2	Weight variation (mg) of 4cm^2	Disintegration Time (sec)	Surface pH	Folding endurance	Drug content
F1	0.652 ±0.00058	0.097 ±0.00458	48	6.79 ±0.0058	25	77.98
F2	0.711 ±0.00058	0.120 ±0.00173	47	6.81 ±0.0100	32	85.71
F3	**0.788 ±0.00058**	**0.134 ±0.00265**	**30**	**6.88 ±0.0153**	**41**	**99.40**
F4	0.672 ±0.00100	0.143 ±0.00265	53	6.87 ±0.0100	28	88.09
F5	0.780 ±0.00058	0.140 ±0.00300	49	6.91 ±0.0058	35	79.76
F6	0.753 ±0.00058	0.152 ±0.00265	38	6.88 ±0.0058	48	97.61
F7	0.814 ±0.00100	0.148 ±0.00173	60	6.89 ±0.0153	67	82.74
F8	0.902 ±0.00153	0.155 ±0.00265	47	6.85 ±0.0058	99	84.52
F9	0.866 ±0.00120	0.180 ±0.00361	40	6.79±0.0322	93	95.24

Table – 3. Result of tensile strength and % elongation of all formulations of 4cm^2 piece

Formulation code	Tensile strength (kg.f/cm^2)	% Elongation
F1	247.45 ±0.27538	20.17 ±0.289
F2	306.12 ±0.44377	27.83 ±0.289
F3	**341.84 ±0.07937**	**33.50±0.500**
F4	364.79 ±0.16503	23.83 ±0.289
F5	357.14 ±0.45574	29.17±0.289
F6	387.75 ±0.15044	25.83±0.289
F7	377.55 ±0.13503	38.00 ±0.500
F8	395.41 ±0.13317	56.00 ±0.500
F9	459.18 ±0.12097	47.17 ±0.289

Each value is the mean ± SD, n = 3 determinations

Tensile strength (TS) and % Elongation:

The tensile strength (TS) gives an indication of the strength and elasticity of the film reflected by the parameters, tensile strength (TS)and elongation at break (E/B). A weak and soft polymer is

characterized by a low TS and E/B; a hard and brittle polymer shows a moderate TS and low E/B; a soft and tough polymer is characterized by a moderate TS and high E/B whereas a hard and tough polymer shows a high TS and E/B. The results showed that among the formulations F3 having tensile strength and % elongation increased with the increase in the percentage of mucoadhesive polymers, HPMC E-15 and MCC. Tensile strength was found to be in the range of 245.45 to 459.18 kg.f/cm^2.The % elongation was found to be in the range of 20.17 to 56.00%.

Table – 4. Results of *in vitro* drug release studies of formulations

Time (min)	Percentage drug released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	9.64	7.49	**12.86**	3.21	8.57	10.71	5.36	2.14	6.43
2	16.07	14.99	**20.36**	8.57	17.14	19.29	13.93	7.49	9.64
3	27.86	24.64	**33.21**	21.43	28.93	33.21	23.57	21.43	24.64
4	39.64	36.43	**39.64**	34.29	42.86	46.07	36.43	26.79	38.57
5	54.64	45.32	**48.21**	56.79	54.64	58.93	53.57	43.93	51.43
6	66.43	63.21	**65.36**	74.99	61.07	68.57	58.93	50.36	58.93
7	71.79	73.93	**72.86**	80.36	70.71	83.57	76.07	64.29	76.07
8	79.29	86.79	**81.43**	92.14	78.21	85.71	82.49	72.86	84.64
9	85.71	88.92	**96.43**	95.36	87.86	94.29	90.00	87.86	92.14
10	91.07	95.36	**99.64**	96.43	92.14	98.57	93.21	95.36	97.49

Each value is the mean ± SD, n = 3 determinations

Table – 5. Kinetic release models for losartan Potassium fast dissolving film

Model		Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order	R^2	0.9786	0.9849	0.9928	0.9550	0.9879	0.9786	0.9826	0.9942	0.9873
First order	R^2	0.968	0.9175	0.7235	0.9450	0.9458	0.8745	0.9469	0.8444	0.8799
Higuchi	R^2	0.9838	0.9692	0.9683	0.9615	0.9911	0.9872	0.9785	0.9628	0.9758
Korsemeyer peppas	R^2	0.987	0.9942	0.9913	0.9749	0.9919	0.9907	0.9902	0.9833	0.9746

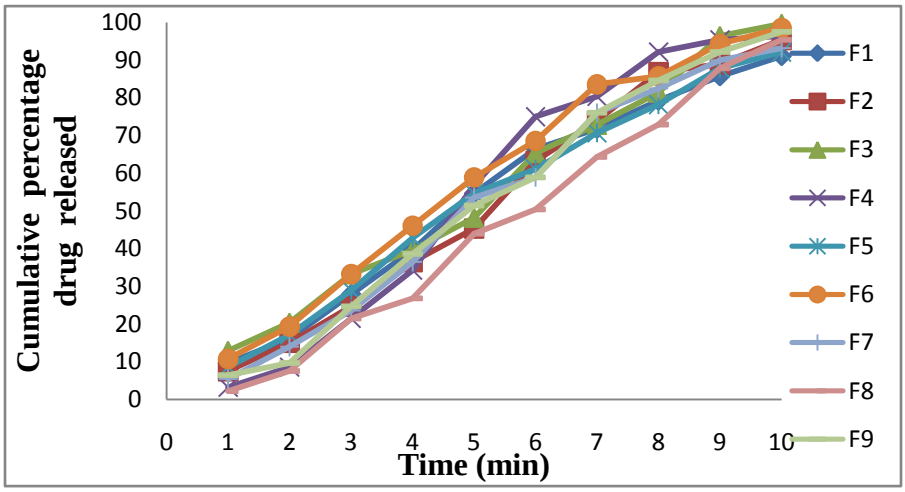


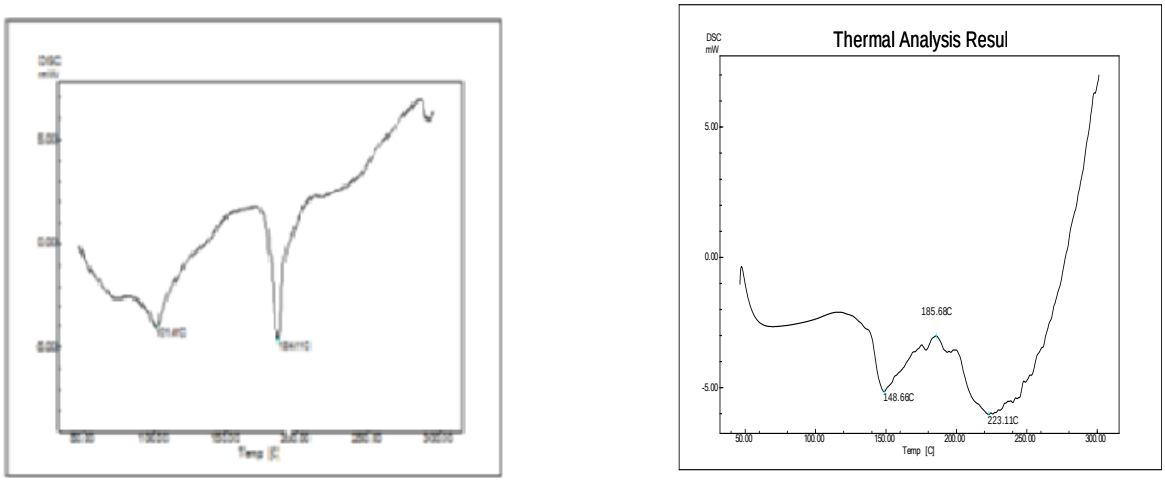
Figure – 1. In vitro release profile of Losartan potassium in simulated salivary fluid

Kinetic analysis of *in vitro* release data:

In order to determine the release mechanism that provides the best description pattern of drug release, the *in vitro* release data were fitted to zero-order, first-order, Higuchi matrix model and Korsmeyer–Peppas model. The release data were matched kinetically with Korsmeyer–Peppas model.

Drug – Polymer interaction studies:

As per DSC study of drug shows the characteristic peak at 184.11˚C as its melting point is 182-184 ˚C reported. The figure - 2 shows the characteristic peak of Losartan Potassium alone. The figure shows the combined peaks of Losartan Potassium and polymers.DSC study of drug and film shows sharp peak at 184.11 and 185.68 ^{o}c respectively. This confirmed drug compatibility with polymer. All the peaks are present in graph and hence the Losartan Potassium is not being interfered due to presence of other Excipients.



Losartan potassium **Film Formulation – F3**

Figure – 2. DSC curves of Losartan potassium and film formulation F3

CONCLUSION:

This investigation shows that fast dissolving films of losartan potassium with the intention of obtaining better therapeutic efficiency by controlling drug release thereby improving patient compliance and increasing bioavailability with decreased dosing and fewer side effects. From the present investigation it can be conclude that fast dissolving films of losartan potassium can be a potential novel drug dosage form for pediatric, geriatric and also for general population.

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